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MAJOR ARTICLE

Relative Effectiveness of Cell-Based Versus Egg-Based Quadrivalent Influenza Vaccines in Adults During the 2019–2020 Influenza Season in the United States

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Background. Mutations occurring during egg-based influenza vaccine production may affect vaccine effectiveness. The mammalian cell-based quadrivalent inactivated influenza vaccine (IIV4c) demonstrated improved protection relative to egg-based vaccines in prior seasons. This study estimated the relative vaccine effectiveness (rVE) of IIV4c versus standard-dose egg-based quadrivalent inactivated influenza vaccine (IIV4e) in preventing influenza-related medical encounters (IRMEs) in the 2019–2020 US influenza season.

Methods. This retrospective cohort study was conducted using a dataset linking electronic medical records with medical and pharmacy claims data among individuals ≥18 years vaccinated with IIV4c or IIV4e during 2019–2020. A doubly robust inverse probability of treatment weighting model was used to obtain odds ratios (ORs) adjusted for age, sex, race, ethnicity, region, vaccination week, health status, frailty, and baseline healthcare resource utilization. rVE was calculated by (1 – OR) × 100. An exploratory analysis evaluated IRMEs in inpatient and outpatient settings separately.

Results. The final study cohort included 1 499 215 IIV4c and 4 126 263 IIV4e recipients ≥18 years of age. Fewer IRMEs were reported in individuals with recorded IIV4c versus IIV4e. The rVE for IIV4c versus IIIV4e for any IRME was 9.5% (95% confidence interval [CI], 7.9%–11.1%). Inpatient and outpatient rVEs were 5.7% (95% CI, 2.1%–9.2%) and 11.4% (95% CI, 9.5%–13.3%), respectively. In age subgroup analyses, rVEs favored IIV4c except in adults aged ≥65 years.

Conclusions. Adults vaccinated with IIV4c had a lower risk of IRMEs versus IIV4e recipients in the 2019–2020 US influenza season. These results support IIV4c as a potentially more effective public health measure against influenza than egg-based vaccines.

Keywords. cell-based influenza vaccine; egg-based influenza vaccine; influenza; quadrivalent inactivated influenza vaccine; relative vaccine effectiveness.

Seasonal influenza causes substantial morbidity and mortality in the United States (US) and worldwide [1, 2]. The US Advisory Committee on Immunization Practices recommends annual vaccination to reduce the impact of influenza on public health [3]. Despite these measures, the effectiveness of vaccines varies across seasons depending on factors such as the antigenic drift of the circulating virus [4, 5]. In addition, traditional egg-based manufacturing of influenza vaccines may also contribute to reduced vaccine effectiveness. During viral propagation within embryonic eggs, mutations in the viral hemagglutinin protein accumulate due to selection pressures, and these changes may alter antigenicity [4, 6, 7]. The possibility of egg-adaptive mutations is eliminated when vaccine viruses are propagated in mammalian cell culture, producing vaccine strains more antigenically similar to the seed-strain virus [8–10].

The first cell-based inactivated quadrivalent influenza vaccine (IIV4c) (Flucelvax Quadrivalent, Seqirus USA Inc, Summit, New Jersey), received initial approval in the US in May 2016 [11]. Observational studies have subsequently provided evidence that cell-based vaccines may have greater effectiveness than traditional egg-based vaccines, particularly in seasons during which egg adaptations affected IIV4e vaccines [12–16].

Given the seasonal circulation of influenza viruses and the associated annual reformulation of influenza vaccines, timely annual estimation of vaccine effectiveness in real-world conditions is important. Building on previous work [15, 16], we conducted a large retrospective cohort study to assess the real-world effectiveness of IIV4c relative to egg-based inactivated quadrivalent influenza vaccine (IIV4e) in preventing influenza-related medical encounters (IRMEs) during the 2019–2020 US influenza season.

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METHODS

Study Design

This retrospective cohort study was conducted in the US during the 2019–2020 influenza season. The primary analysis study period was from 1 August 2019 through 7 March 2020. This aligns with the Centers for Disease Control and Prevention (CDC) influenza surveillance season, defined as epidemiologic weeks 40 through 20 of the subsequent year, though we truncated the end of the study period to avoid potential bias arising from the co-circulation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the US in March 2020.

Data Sources and Linkage

The dataset used in the analysis was an integrated dataset of patient-level electronic medical records (EMRs) from primary care and specialty clinics, linked with pharmacy and medical claims data for approximately 123 million individuals from all 50 US states. The integrated dataset provides comprehensive pharmaceutical, demographic, diagnostic, and healthcare utilization information. Three national EMR systems form the basis of the integrated dataset (ie, Veradigm Health Insights Ambulatory database): Allscripts Professional and Allscripts Touchworks (Chicago, Illinois) and Practice Fusion (San Francisco, California). These datasets include medical practices of a range of sizes: small practices (1–3 physicians), medium-sized practices (4–40 physicians), and integrated delivery networks. The Komodo Healthcare Map (Komodo Health Inc, New York, New York) consists of anonymized patient-level US pharmacy and medical claims. Both open and closed claims were utilized in this analysis. Data from open claims are sourced from practice management systems, billing systems, and claims clearinghouses and provide a view of the patient journey over a longer period of time, whereas closed claims are sourced from insurance providers and payers and encompass a more complete view of a patient's interactions with the healthcare system within a set time frame for which patient enrollment/eligibility information in the health plan is available. Prior to linkage, each individual dataset underwent de-dentification and privacy certification to verify it met the minimum Protected Health Information data requirements. The dataset was also evaluated and certified for Health Insurance Portability and Accountability Act (HIPAA) compliance by a third-party statistician (see Supplementary Data for de-identification and linkage details).

Exposure Ascertainment

Current Procedural Terminology codes, codes for vaccines administered, and national drug codes (Supplementary Table 1) were used to identify vaccinated subjects from both EMRs and claims data within the vaccination intake period. The exposure of interest was unadjuvanted, standard-dose IIV4c, which was compared to unadjuvanted, standard-dose IIV4e. Individuals receiving enhanced vaccines were not included. The date of recorded vaccination with either IIV4c or IIV4e was considered the index date.

Study Population

The study population for the current analysis included US residents ≥18 years of age who had received either IIV4e or IIV4c between 1 August 2019 and 31 January 2020 (vaccination intake period). Children and adolescents 4 to 17 years of age were also evaluated, and results have been reported elsewhere [17]. Subjects needed to have activity in the Veradigm EMR as well as the claims database within the 12 months prior to the index date to be included in the analysis. Subjects were excluded if they had a record of >1 influenza vaccination during the season period, had a record of influenza vaccination outside the vaccination intake period, or had an IRME during the 2019–2020 season prior to being considered vaccinated. Subjects were considered vaccinated 14 days after index date to allow for development of vaccine-specific immunity. Subjects who had an IRME prior to the start of influenza season (ie, prior to 29 September 2019) and after the end of the previous influenza season and those with missing sex or geographic information were also excluded from the analysis.

Outcome Ascertainment

The outcome of interest was the occurrence of an IRME ascertained using *International Classification of Diseases* (*ICD*) codes for influenza disease as reported by the Armed Forces Health Surveillance Center Code Set B case definition (Supplementary Table 2) [18]. Of note, for inpatient IRMEs, results are presented separately for an influenza diagnosis as the admitting diagnosis and an influenza diagnosis in any diagnostic position within the medical claim. The "admitting diagnosis" is the initial working diagnosis for which an individual was admitted, whereas "any diagnosis" includes secondary diagnoses, that is, conditions that coexisted at the time of admission or developed subsequently. IRMEs recorded during an emergency department visits were classified as inpatient. The follow-up period lasted either until a record of an IRME or the end of the observation period (7 March 2020).

Covariates

Covariates were identified in the 12 months prior to the index date and included age, sex (male, female), race (Black, White, not reported, other), ethnicity (Hispanic, non-Hispanic, not reported), US geographic region (Northeast, Midwest, South, West, other), index week, frailty index (a summary score for activities of daily living [19]; Supplementary Table 3), individual comorbidities included in the Charlson Comorbidity Index (CCI [20, 21]; Supplementary Table 4), number of outpatient visits in the 12 months prior to the recorded vaccination

date, and number of inpatient admissions in the 12 months prior to the recorded vaccination date.

Statistical Methods

Differences in baseline covariates between the exposure groups were assessed using standardized mean difference (SMD), with a value of ≤0.1 indicating a negligible difference. Categorical variables with missing or null values were classified as "not reported/unknown"; missing or out-of-range values were not imputed.

Inverse probability of treatment weighting (IPTW) was implemented to adjust for covariate imbalance between the vaccine cohorts [22]. In the IPTW method, weights are assigned to individuals based on the inverse of their probability of receiving the vaccine, as estimated by propensity scores (PSs). First, PSs were calculated for each exposure cohort using a multivariable logit model adjusted for all covariates listed above. PSs were then used to create stabilized IPTWs. Weights were truncated at the 99th percentiles to attenuate any extreme variability from outlier patients. Adjusted odds ratios (ORs) were estimated using a doubly robust approach. Final adjusted ORs were estimated for the IPTW-weighted cohorts using a multivariable logistic regression model, including all variables in the PS model [23]. rVE was calculated as 100 × (1 – adjusted OR) and is reported with 95% confidence intervals (CIs). Analyses were repeated for each age subgroup (18–64 years, 18–49 years, 50–64 years, ≥65 years) for which weights were redrawn for each age subgroup. The main outcome concerned IRMEs in any setting. In an exploratory analysis, inpatient and outpatient IRMEs were analyzed separately. Analyses were conducted using SQL and SAS software (version 9.4).

Sensitivity analyses were conducted to assess the robustness of study assumptions. First, the moving epidemic method restricted the rVE analysis to the period of highest incidence of laboratory-confirmed influenza (ie, 8 December 2019 through 7 March 2020) to aim to improve the specificity of case definitions. Second, 2 analyses were conducted to account for the impact of coronavirus disease 2019 (COVID-19): 1 with an early study period cutoff, prior to widespread COVID-19 circulation (29 September 2019 through 15 February 2020) and another that extended through the full influenza season (29 September 2019 through 16 May 2020) to assess impact of COVID-19 on effect estimates. Finally, in a negative control outcome analysis, urinary tract infections (UTIs; defined by *ICD, Tenth Revision* N39.0 codes) were evaluated as the main outcome to assess balance among cohorts as well as indicate residual bias in effect estimates. A Cox regression model was used to evaluate UTIs to factor in the seasonal variability in the frequency of UTIs [24–26]. The study was designed, implemented, and reported in accordance with Good Pharmacoepidemiological Practice, applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki. Study results have been reported according to the Reporting of Studies Conducted using Observational Routinely Collected Health Data (RECORD) recommendations. Because this study was a noninterventional, retrospective study using a certified HIPAA-compliant database, approval for this analysis by an institutional review board was not necessary.

RESULTS

Study Subjects

Table 1 and Supplementary Tables 4–5 list the demographic and clinical characteristics of the study population. Of 5 625 478 individuals included in the study, 1 499 215 (26.7%)

Table 1. Subject Demographics at Baseline

Characteristic	IIV4c (n = 1 499 215)	IIV4e (n = 4 126 263)	SMD
Age, y, mean ± SD	54.1 ± 16.5	51.2 ± 16.3	0.09
18–64 y	1 144 427 (76.3)	3 427 818 (83.1)	…
18–49 y	533 073 (35.6)	1 726 866 (41.9)	…
50–64 y	611 354 (40.8)	1 700 952 (41.2)	…
≥65 y	354 788 (23.7)	698 445 (16.9)	…
Female sex, No. (%)	925 353 (61.7)	2 536 169 (61.5)	0.00
Race and ethnicity			
Black or African American	88 032 (5.9)	226 502 (5.5)	0.00
White	685 650 (45.7)	1 960 748 (47.5)	−0.03
Other	199 581 (13.3)	524 936 (12.7)	0.01
Not reported	525 952 (35.1)	1 414 077 (34.3)	0.02
Hispanic	97 976 (6.5)	258 331 (6.3)	0.01
Non-Hispanic	1 291 870 (86.2)	3 465 820 (84.0)	
Not reported	109 369 (7.3)	402 112 (9.7)	
Geographic region			
Northeast	313 499 (20.9)	881 539 (21.4)	0.04
Midwest	177 683 (11.9)	985 614 (23.9)	−0.13
South	770 272 (51.4)	1 381 230 (33.5)	0.07
West	235 885 (15.7)	870 617 (21.1)	0.02
Other	1876 (0.1)	7263 (0.2)	0.00
CCI ± SD	1.0 ± 1.6	0.9 ± 1.5	0.02
Frailty index[a], mean ± SD	0.17 ± 0.20	0.19 ± 0.22	−0.06
<5%	351 619 (23.5)	977 588 (23.7)	−0.02
5%–19%	796 025 (53.1)	2 016 277 (48.9)	
≥20%	351 571 (23.5)	1 132 398 (27.4)	
Outpatient visits, mean ± SD	1.0 ± 2.4	1.2 ± 2.6	−0.04
All-cause hospitalizations			
0	1 071 995 (71.5)	2 795 750 (67.8)	−0.03
1	251 275 (16.8)	751 782 (18.2)	
≥2	175 945 (11.7)	578 731 (14.0)	
Place of service (data source)			
Pharmacy only claims	556 092 (37.1)	907 168 (22.0)	0.27
Medical claims	847 570 (56.5)	2 859 225 (69.3)	−0.22
EMR-only claims	95 553 (6.4)	359 870 (8.7)	−0.05

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CCI, Charlson comorbidity index; EMR, electronic medical record; IIV4c, cell-based inactivated quadrivalent influenza vaccine; IIV4e, egg-based inactivated quadrivalent influenza vaccine; SD, standard deviation; SMD, standardized mean difference.

[a]Frailty was approximated using a summary score for activities of daily living (ADLs) [19] to represent an operational definition of frailty in claims data using ADL dependency as a proxy outcome (Supplementary Table 3).

received IIV4c and 4 126 263 (73.3%) received IIV4e (Table 2). Subjects who received IIV4c were slightly older than IIV4e recipients (54.1 ± 16.5 vs 51.2 ± 16.3 years of age) but had slightly lower frailty index scores. Across age groups, the proportion of IIV4c use was lower than that of IIV4e. The majority of subjects in both groups were female and non-Hispanic, and racial representation was similar between the groups. The type of vaccine differed in the South and Midwest regions; more than half of IIV4c and one-third of IIV4e recipients resided in the US South, and approximately twice as many IIV4e as IIV4c recipients were from the Midwest. Other between-group SMDs were <0.05 (Table 1 and Supplementary Table 4). Chronic pulmonary disease, diabetes, peripheral vascular disease, and renal disease were the most common medical conditions, with comparable percentages across both exposure groups (Supplementary Table 4).

Overall IRMEs

In the overall population, 19 432 (1.3%) IRMEs occurred in IIV4c recipients and 61 768 (1.5%) in IIV4e recipients. As shown in Figure 1A, in all adults aged ≥18 years, the adjusted rVE was 9.5% (95% CI, 7.9%–11.1%). Among those aged 18–64 years, the rVE was 11.9% (95% CI, 10.2%–13.6%). Estimates for adult age subgroups were 13.1% (95% CI, 10.8%–15.3%) for 18–49 years, 10.5% (95% CI, 7.8%–13.2%) for 50–64 years, and −9.4% (95% CI, −14.2% to −4.7%) for ≥65 years. Unadjusted rVEs for all analyses are shown in Supplementary Figure 1.

Inpatient and Outpatient IRMEs

Overall, 4379 (0.29%) and 14 047 (0.34%) of IIV4c and IIV4e recipients, respectively, were admitted to a hospital for an IRME (admitting diagnosis on the claim). The rVE for the overall study cohort for inpatient outcomes was 5.7% (95% CI, 2.1%–9.2%), and age subgroup rVEs were 5.8% (95% CI, 1.9%–9.5%) in 18–64 years, 6.6% (95% CI, 1.6%–11.3%) in 18–49 years, 5.2% (95% CI, −.9% to 11.1%) in 50–64 years, and 5.3% (95% CI, −4.9% to 14.5%) in ≥65 years (Figure 1B). Slightly more patients were admitted to a hospital with an IRME in any diagnosis position on the claim: 5722 (0.38%) IIV4c recipients and 18 003 (0.43%) IIV4e recipients. The point estimates of rVEs for any inpatient stay associated with an IRME favored IIV4c in all age groups, and the lower limit of the CIs was >1 in younger subjects (≤49 years) and the overall study population (Figure 1C).

Outpatient medical visits were recorded for 13 710 (0.9%) IIV4c and 43 765 (1.1%) IIV4e recipients. The rVEs were 11.4% (95% CI, 9.5%–13.3%) for all subjects aged ≥18 years. The rVE for adult age subgroups was 14.7% (95% CI, 12.7%–16.7%) for 18–64 years, 16.2% (95% CI, 13.5%–18.7%) for 18–49 years, 13.0% (95% CI, 9.8%–16.1%) for 50–64 years, and −14.6% (95% CI, −20.5% to −8.9%) for ≥65 years (Figure 1D).

Table 2. Subject Selection in the 2019–2020 Influenza Season

Selection Criterion	No. of Subjects (%)
1. Patient received an influenza vaccine between 1 August 2019 and 31 January 2020	10 087 998 (100.0)
2. Patient is at least 18 y of age at time of vaccination	7 826 955 (77.6)
3. Patient does not have ≥1 influenza vaccination during the influenza season	7 621 199 (75.5)
4. Patient does not have an IRME prior to becoming fully vaccinated or prior to the influenza season	7 606 191 (75.4)
5. Patient has a transcript record in the Veradigm EMR ≥1 y prior to vaccination date	6 415 648 (63.6)
6. Patient has activity in Komodo claims ≥1 y prior to vaccination date	5 658 709 (56.1)
7. Patient does not have missing or conflicting data for age, sex, or geographic region	5 625 478 (55.8)
IIV4c recipients	1 499 215 (14.9)
IIV4e recipients	4 126 263 (40.9)

Abbreviations: EMR, electronic medical record; IIV4c, cell-based inactivated quadrivalent influenza vaccine; IIV4e, egg-based inactivated quadrivalent influenza vaccine; IRME, influenza-related medical encounter.

Additional Analysis

Due to the differences in vaccine use across regions, post hoc stratification by region as well as setting was undertaken, to further understand the findings among those ≥65 years of age. Regional analyses of inpatient and outpatient IRMEs reflected overall IRME findings in the younger age groups but not in those ≥65 years of age, where a negative overall rVE was driven by the outpatient rVE in the Northeast and most strongly in the West (Supplementary Figure 2).

Sensitivity Analyses

During the period of highest influenza activity (8 December 2019 to 7 March 2020; Supplementary Figure 3), rVE estimates were slightly higher than in the main analysis overall: 10.8% (95% CI, 9.2%–12.5%) in subjects at least 18 years of age and 12.8% (95% CI, 11.0%–14.6%) in those aged 18–64 years; rVE among those ≥65 years of age was −6.6% (95% CI, −11.7% to −1.8%) (Figure 2A).

Prior to the onset of the COVID-19 pandemic in the US (29 September 2019 to 15 February 2020), the rVE was 7.8% (95% CI, 5.9%–9.6%) for the overall population, 10.0% (95% CI, 7.9%–12.0%) for age 18–64 years, and −10.8% (95% CI, −16.5% to −5.4%) for age ≥65 years (Figure 2B). During the full influenza season (through 16 May 2020), rVEs were 9.8% (95% CI, 8.2%–11.4%), 12.1% (95% CI, 10.3%–13.8%), and −8.8% (95% CI, −13.7% to −4.1%) in the respective age groups (Figure 2C).

In the entire study cohort, 3.7% of IIV4c and 3.4% of IIV4e recipients had a record of a UTI during the study period, with a hazard ratio of 1.00 (95% CI, .99–1.02).

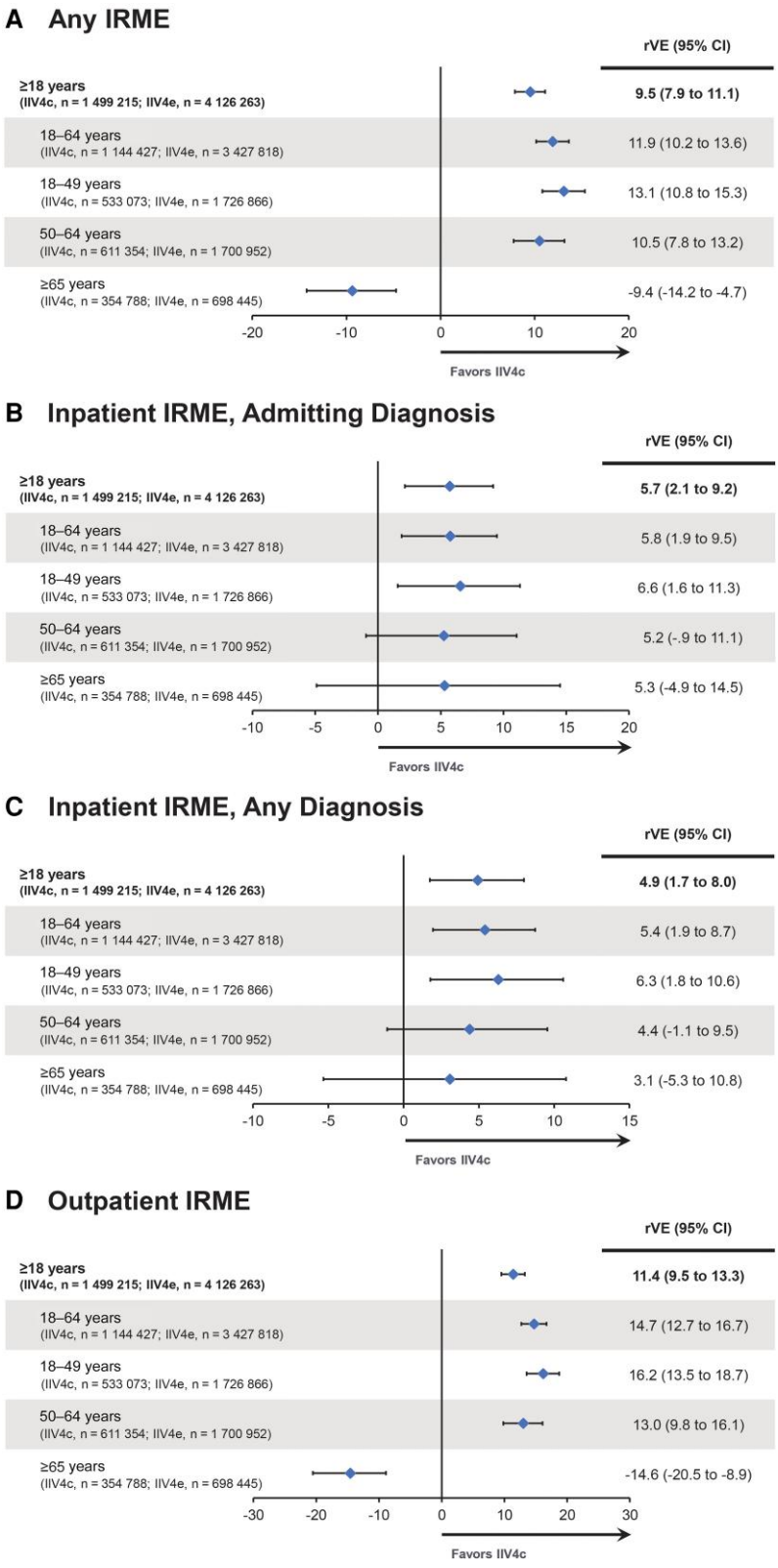

Figure 1. Relative vaccine effectiveness of cell-based inactivated quadrivalent influenza vaccine compared with egg-based inactivated quadrivalent influenza vaccine among individuals aged ≥18 years in the 2019–2020 influenza season using doubly robust inverse probability of treatment weighting adjustment methodology. *A*, Any influenza-related medical encounter (IRME). *B*, IRME reported as admitting diagnosis for a hospital inpatient stay. *C*, IRME reported during any hospital inpatient stay. *D*, IRME reported as an outpatient visit. Abbreviations: CI, confidence interval; IIV4c, cell-based inactivated quadrivalent influenza vaccine; IIV4e, egg-based inactivated quadrivalent influenza vaccine; rVE, relative vaccine effectiveness.

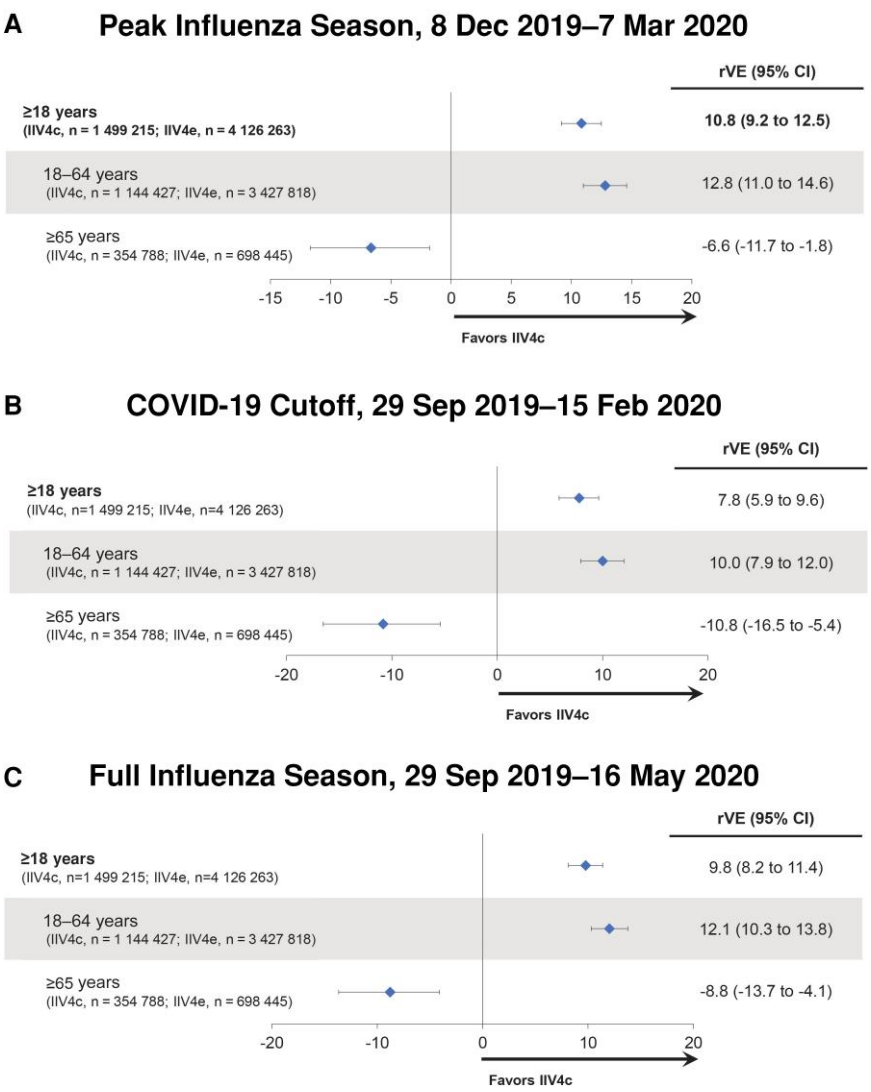

Figure 2. Sensitivity analyses determining relative vaccine effectiveness of cell-based inactivated quadrivalent influenza vaccine compared with egg-based inactivated quadrivalent influenza vaccine among individuals aged ≥18 years in the 2019–2020 influenza season using doubly robust inverse probability of treatment weighting adjustment methodology. *A,* Restricted season with peak influenza activity between 8 December 2019 and 7 March 2020. *B,* Coronavirus disease 2019 onset cutoff analysis, 29 September 2019 through 15 February 2020. *C,* Full influenza season analysis, 29 September 2019 through 16 May 2020. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; IIV4c, cell-based inactivated quadrivalent influenza vaccine; IIV4e, egg-based inactivated quadrivalent influenza vaccine; rVE, relative vaccine effectiveness.

DISCUSSION

In this study, IIV4c conferred a 10% reduction in IRMEs relative to IIV4e in the study population of adults ≥18 years, and results remained consistent during the months of peak influenza activity. These analyses were conducted during a season in which the predominant circulating strain in adults was A(H1N1)pdm09 along with B/Victoria co-circulation (Supplementary Figure 3) [27]. The US CDC estimated overall absolute vaccine effectiveness (aVE) for all influenza vaccines to be 39% (95% CI, 32%–44%) in the 2019–2020 season; aVE in adults ranged between 34% and 40% [28]. Adaptive viral mutations can occur during propagation of influenza vaccine viruses in embryonated chicken eggs, which may impact antigenicity [29–31]. In contrast, virus propagation in mammalian cells eliminates the potential for egg adaptation [6]. For A(H1N1)pdm09 viruses, 6B.1A subclades 5A, 5B, and 7 predominated globally whereas the vaccine virus was clade 6B.1A1, indicating genetic drift [32]. While the CDC found that circulating and vaccine A(H1N1) viruses were antigenically similar based on antigenic characterization with ferret antisera, the WHO stated that based on human serology studies, circulating A(H1N1) viruses had decreased antigenic similarity to cell-propagated reference virus and even more pronounced differences when compared to an egg-propagated reference

virus, indicating potential egg adaptation [32–34]. Among B/Victoria viruses, clade V1A.3 viruses predominated (97%), but the vaccine virus belonged to the V1A.1 clade [33]. Fewer circulating B/Victoria viruses were antigenically similar to the egg-propagated vaccine reference virus compared to the cell-propagated vaccine reference virus (60% vs 8%, respectively) [35]. However, the B/Victoria vaccine virus provided good cross-protection as indicated by the CDC's estimate of a strain-specific aVE (45%) for B/Victoria, which is consistent with the aVE during seasons where B/Victoria vaccine virus was well matched to circulating viruses [28]. Our findings suggest that cell-based vaccines may provide better protection than egg-based vaccines even during seasons without significant A/H3N2 circulation, the strain which is known to be particularly impacted by egg-adaptive changes.

IRMEs recorded in inpatient settings were significantly reduced among those <50 years of age, and outpatient visits were decreased significantly among those aged ≤64 years. The CDC estimate of absolute vaccine effectiveness in persons aged 18–49 years was 34% (95% CI, 23%–44%) [28]. In our study, this age cohort experienced the greatest reduction in both inpatient admissions and outpatient visits with IIV4c versus IIV4e. Absolute vaccine effectiveness against A/H1N1 was 40% in those 50–64 years of age and 42% in those 65 years and older [28]. In our study, an rVE of 10.5% (95% CI, 7.8%–13.2%) was observed for IIV4c versus IIV4e in those aged 50–64 years.

For the age group ≥65 years, the age subgroup analysis did not suggest a consistent benefit for IIV4c versus IIV4e. Our results did not show a benefit of IIV4c for adults ≥65 years against any IRME. There were no significant differences in age, CCI, or frailty index between IIV4c and IIV4e recipients in those aged ≥65 years. An rVE in favor of IIV4e for this age group was observed in the outpatient settings, whereas the rVE for inpatient settings suggested similar benefit for both vaccines. The inpatient rVE was consistent with rVEs estimated in previous seasons using the same dataset in the age group ≥65 years [15, 16]. A possible explanation for this observation is that the spread of COVID-19 coincided with the 2019–2020 influenza season and resulted in changes to healthcare-seeking behavior, especially in the age group ≥65 years, as steps were undertaken to reduce the risk of contact for both patients and healthcare professionals. Therefore, results in this age subgroup could be the result of confounding related to the evolving COVID-19 pandemic [12]. Although the sensitivity analysis using conservative cutoff dates to account for COVID-19 impact do not suggest this, there is still a possibility of misclassification of SARS-CoV-2 as influenza, as SARS-CoV-2 may have been circulating earlier in the season when coding practices for COVID-19 had not yet been established.

Influenza vaccines require at least yearly reformulation to keep pace with the antigenic drift of circulating strains. Furthermore, the presence of egg adaptation and the extent of egg adaptation also varies from year to year. Therefore, it is important to assess rVE during each influenza season. Although research on previous seasons has been conducted, there is limited evidence on the 2019–2020 influenza season on the rVE of IIVc versus IIV4e. Existing evidence differed with respect to study population, setting, influenza case definition, and methodological aspects [36–39]. The current study adds to the body of evidence on the rVE of IIV4 versus IIV4e in the 2019–2020 season for individuals ≥18 years of age in the US.

A strength of this study was the use of a large, integrated dataset linking EMRs with claims data A large, inclusive study population enabled robust statistical power to detect differences in healthcare settings representative of real-world conditions. The variety and completeness of these data permitted for adjustment of well-established confounders using a doubly robust IPTW methodology. Consistent results were demonstrated across sensitivity analyses. In addition, the negative control analysis showed no difference in performance of the 2 vaccines in the incidence of UTIs, a condition unrelated to influenza.

The study has several limitations. We did not include a laboratory-confirmed study outcome, although results were consistent when limited to the period of a high incidence of laboratory-confirmed influenza (Figure 2*A*) [27]. Moreover, incidence rates of laboratory-confirmed influenza reported by the CDC showed a similar trend when compared to frequency of IRMEs in the study cohort over time (Supplementary Figure 3) [27]. The study population was limited to insured persons for whom pharmacy and medical claims data were available and did not capture data on uninsured individuals. Finally, as with all observational studies, there is a possibility of residual confounding bias.

CONCLUSIONS

This analysis of a large integrated EMR and medical claims database demonstrates that IIV4c was associated with fewer IRMEs than IIV4e in adults ≥18 years of age during the 2019–2020 influenza season in the US. These findings support those from previously published work demonstrating that IIV4c may be more effective at preventing influenza than an egg-based equivalent [12, 13, 40–43].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. I., C. B., and J. A. M. were involved in study conception, design, and conceptual frameworks. L. F., D. O., and

M. B. were involved in the analysis. H. Q. M. and J. R. O. provided regular feedback on each of these steps. All authors were involved in the interpretation of data. M. I. and C. B. were involved in drafting the manuscript and L. F., D. B., M. B., J. A. M., H. Q. M., and J. R. O. revised the paper critically. All authors made substantive intellectual contributions to the development of this manuscript and approved the final version.

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Patient consent. This retrospective cohort study did not include factors necessitating patient consent.

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Potential conflicts of interest. M. I. and C. B. are employees of Seqirus Inc. J. A. M. was an employee of Seqirus during study conduct. J. R. O. reports receiving grants to his institution from the National Institutes of Health for influenza vaccine research; grants to his institution from GSK, Pfizer, and PATH for vaccine (noninfluenza) research; and honoraria from Seqirus to serve on the Real World Evidence Scientific Advisory Board and from Pfizer to serve on the Immunization for All Ages Advisory Board. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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